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Analyses of HIV-1 Viral Dynamics During Treatment With a Regimen Including an Integrase Inhibitor

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BACKGROUND

Viral dynamics analyses of HIV infection have provided insights into the viral replication process

Hypothesis

- Analysis and modeling of HIV dynamics during therapy including an integrase inhibitor (InSTI) will reveal new details of the viral decline and the viral life cycle.

Aims

- Develop a dynamical model that specifically accounts for the effect of InSTI.
- Analyze patient data on treatment with InSTI.
- Understand the dynamics of integration.

EXPERIMENTAL METHODS

We analyzed data from a clinical trial

ACTG A5249s

- This is an intensive sampling viral dynamics substudy of ACTG A5248.
- Eleven HIV-1-infected, ARV-drug naïve subjects, with baseline viral loads between 10^4 and $3x10^5$ copies/ml.
- No evidence of resistance (for reverse transcriptase and protease inhibitors) by genotype screening.
- Treated with raltegravir (RAL) (400mg PO BID) + FTC/TDF (200mg/ 300mg PO QD).
- VL measurements at 0, 2, 4, 6, 12, 18, 24,30, 36, 42, 48h post-treatment and then on days 3, 4, 7, 10, and 14.
- HIV-1 RNA was assayed with the Roche Ultrasensitive assay with limit of detection of 50 copies/ml.

The data

- The initial decline over the first week is not a single phase of decay as observed previously with RTI and PI combinations [1].
- The initial phase of decline is biphasic (phase 1a and 1b) with a first phase (1a) lasting 2-5 days followed by a slower phase (1b) of viral decline.

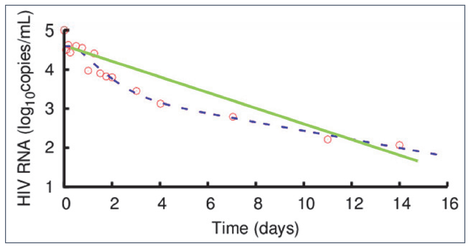
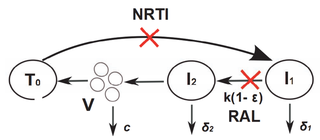


Figure 1. Viral load data (red symbols) and viral load decline assuming a single phase (green line) or two phases (blue line) of viral decline

- What do phases 1a and 1b represent ?

MODEL



T – target cells
I_1 – Infected cells without integrated HIV DNA
I_2 – Productively infected cells
V – free virus

Model

- The basic model with a single infected cell compartment has been used successfully to analyze HIV dynamics under treatment [1].
- To model the effect of RAL, we separate infected cells into two compartments [2,3]: I_1 – cells without integrated DNA; and I_2 – productively infected cells.
- RAL therapy is modeled by assuming it reduces the transition from I_1 to I_2, from k to k(1-ε), where 0<ε<1.
- RT inhibitors are modeled in the usual way, assuming they reduce infectivity (i.e., generation of I_1) by (1-η).
- Assuming that target cells, T, remain approximately constant during the first two weeks of therapy at T_0 [1], we have

$$\frac{dI_1}{dt} = (1-\eta)\beta T_0 V - \delta_1 I_1 - k(1-\varepsilon)I_1$$
$$\frac{dI_2}{dt} = k(1-\varepsilon)I_1 - \delta_2 I_2$$
$$\frac{dV}{dt} = pI_2 - cV$$

- Redefine variables such that $I_1 = p\, I_1$, $I_2 = p\, I_2$, and $T_0 = \beta\, p\, T_0$; and make the usual assumption of quasi steady state (i.e., $I_2 = c\, V$), to simplify to

$$\frac{dI_1}{dt} = (1-\eta)T_0 V - \delta_1 I_1 - k(1-\varepsilon)I_1$$
$$\frac{dV}{dt} = \frac{k}{c}(1-\varepsilon)I_1 - \delta_2 V$$

- This model predicts two phases of decline.

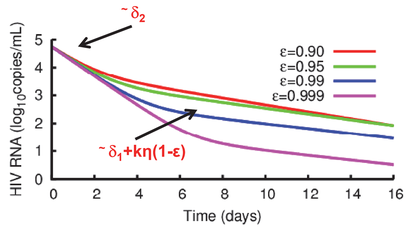


Figure 2. Viral load decline predicted by the model for different values of RAL effectiveness

- If we consider that the dynamics of I_1 are much slower than those of V, we can hold I_1 approximately constant at its pre-treatment value, $\delta_2 c V_0 / k$, and find that, early on, the viral load is given by

$$V(t) \approx V_0(1-\varepsilon+\varepsilon e^{-\delta_2 t})$$

- The extent of the decay in phase 1a is given by (1-ε), and thus the magnitude of the decline is a direct measure of the effectiveness of an InSTI, as has been found for HCV antivirals [4].

DATA ANALYSIS

The solution of the model is

$$V(t) = \frac{V_0\, e^{-\frac{(t-t_0)}{2}(\alpha+\delta_2+\theta)}}{2\theta}\left[\left(e^{\theta(t-t_0)}-1\right)\left(\alpha+\delta_2(1-2\varepsilon)\right)+\left(e^{\theta(t-t_0)}+1\right)\theta\right]$$

- With $\alpha = k(1-\varepsilon) + \delta_1$ and $\theta = \sqrt{(\alpha-\delta_2)^2 + 4k\frac{T_0}{c}(1-\eta)(1-\varepsilon)}$
- In addition, this solution considers a pharmacokinetic delay (t_0) before the effect of the drug is felt. During this time $V(t)=V_0$.

Data fits

- Data were fitted using nonlinear mixed effect models, an approach which fits all subjects together to precisely estimate the mean and the between-subject variability.
- We assumed a constant error model for $\log_{10}$ of HIV RNA.
- Data were analyzed using MONOLIX 4.2.0.
- The viral clearance rate, c, was fixed to 23 d^{-1} [5].

Results

t_0 (day)	k (day^{-1})	ε	η	δ_1 (day^{-1})	δ_2 (day^{-1})
0.51 (0.11)	1.71 (1.9)	0.95 (0.023)	0.93 (0.13)	0.16 (0.052)	0.93 (0.094)

Table 1. Estimates of the viral kinetic parameters (standard error)

- The model described the data well for all patients (Fig 3)
- RAL effectiveness in blocking DNA integration was 95%.
- The loss rate of productively infected cells was 0.93 d^{-1}.
- The loss rate of cells without integrated DNA was 0.16 d^{-1}

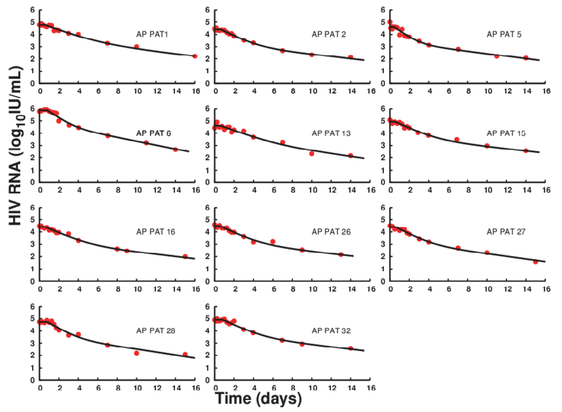


Figure 3. Viral load data (red symbols) and dynamics predicted by the model (solid line) using the best parameter estimates from the population fits

RESULTS & DISCUSSION

Results

- The kinetics of viral decline was biphasic in all patients, with a rapid 1st phase followed by a 2nd slower phase.
- In our model, this feature is attributed to the high effectiveness of RAL in blocking viral integration (95%).
- The first phase, 1a, is due to the rapid elimination of productively infected cells, just as in the standard model.
- The slower phase, 1b, is due to the small number of cells for which RAL was unable to prevent productive infection
- k was estimated as 1.7 d^{-1}, corresponding to a half-life for the integration of viral DNA of 9.7 h, which is in agreement with prior in vitro findings (Fig 4).

Discussion

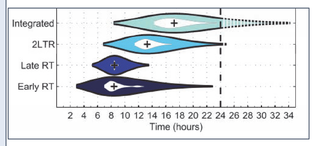


Figure 4. Estimated time between different phases of HIV-1 lifecycle (from [6]). Note that the time from reverse transcription to integration is ~9 h (comparing the peak of activity, "+"), but there is a large uncertainty (shaded area corresponds to 98% quantile for each phase).

- k had a large uncertainty (standard error), thus we also fitted the data fixing k at different values in [0.1-10]. We obtained similarly good fits to the data; and values of η in [0.8-1], δ_1 in [0.12-0.23 d^{-1}], δ_2 in [0.84-0.95 d^{-1}] and ε in [0.95-0.98].
- A study with more patients and additional data will be needed to confirm our parameter estimates.
- A limitation is that the model does not include long-lived infected cells, which also are a source of biphasic declines [7].
- The effect of this reservoir will need to be included in future models, possibly using longer term data for these patients from the parent study, ACTG A5248 [8].

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